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Damaged DNA and Miscounted Chromosomes: Human T Cell Leukemia Virus Type I Tax Oncoprotein and Genetic Lesions in Transformed Cells

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Abstract
Genetic instability is a recurring theme in human cancers. Although the molecular mechanisms mediating this effect commonly observed in transformed cells are not completely understood, it has been proposed to involve either the loss of DNA repair capabilities or the loss of chromosomal stability. The transforming retrovirus human T cell leukemia virus type I (HTLV-I) encodes a viral oncoprotein Tax, which is believed to cause the genomic instability characteristic of HTLV-I-infected cells. This review focuses on the ability of HTLV-I Tax to disrupt the cellular processes of DNA repair and chromosomal segregation. The consequences of these effects as well as the evolutionary advantage this may provide to HTLV-I are discussed.

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Genetic Basis of Cancer

Although the minimal requirements for the transformation of human cells remain incompletely understood [32], genetic and phenotypic instability are characteristics common to all types of human cancers. Human neoplasia is the product of a complex multistep process involving changes in many cellular genes. It has been suggested that tumors may contain more than 100,000 discrete mutations [47], generated via clastogenic events that give rise to chromosome breakage or mutation and aneuploidogenic events that result in a nonhaploid chromosome number or inaccurate chromosome segregation. Although many different types of cancers exist, mechanistically, one can broadly categorize all cancers into two groups: those with loss of DNA repair function and those with chromosomal instability [reviewed in ref. 36].

Statistically, approximately one third of all individuals in the developed world will develop cancer in their lifetimes [71]. The vast majority of these cancers occur in older adults, implying that a subpopulation of cells over a human life span is surprisingly susceptible to genetic changes. From large surveys of human neoplasms, it can be concluded that aneuploidy is a recurring feature seen in

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70–80% of all cancers [15]. Because aneuploidy is an efficient means of quickly creating wholesale changes in numerous genes and because (as mentioned above) numerous changes are necessary to convert a normal cell into a cancer cell, the prevalence of aneuploidy in cancers makes sense. Indeed, emerging evidence suggests that aneuploidy may initiate tumor formation as well as drive tumor progression [30, 32].

The human T cell leukemia virus type I (HTLV-I) retrovirus has been implicated as the etiologic agent of adult T cell leukemia (ATL) [17, 51, 72]. This rapidly progressing malignancy of mature CD4+ T cells presents 20–40 years after viral infection and in less than 5% of all infected individuals. While integration of the HTLV-I provirus occurs randomly, transformed cells from an individual patient display a clonal pattern of proviral insertion, suggesting that transformation is a rare event among all infected cells. Both HTLV-I-transformed lymphocytes isolated from patients and those immortalized in culture contain a large percentage of chromosomal aberrations, including translocations, rearrangements, duplications and deletions [6, 12, 20, 23, 40, 42, 55, 56, 64, 70]. To date, however, no specific chromosomal abnormality has been associated with the development of ATL. Here, using ATL as an example, we review in a nonexhaustive fashion the mechanisms utilized by the HTLV-I Tax oncoprotein to engender genetic lesions which likely account for cellular transformation.

Clastogenic Effects of the HTLV-I Tax Protein

Evidence of both clastogenic and aneuploidogenic damage exists in HTLV-I-transformed cells. Clastogenic events (point mutations, deletions, substitutions, translocations) typically result from combined defects in DNA repair mechanisms and cell cycle checkpoints and will be considered first in this review. The transforming properties of HTLV-I have most frequently been attributed to the viral Tax protein [13, 16, 45, 53, 63]. Tax is a multifunctional protein that can regulate the transcriptional activity of a select subset of cellular genes responsible for cell growth control [reviewed in ref. 11, 29, 54]. Tax also has posttranscriptional effects on the activity of specific cellular proteins, including p53 and $p16^{INK4a}$, which regulate cell growth and responses to DNA damage [4, 38, 49, 50, 60, 61]. Despite its diverse biological functions, there is no evidence that Tax actually *causes* DNA damage [57]. Rather, Tax appears to inhibit the cell's ability to repair DNA damage that has been introduced from various environmental sources, resulting in an increased mutation frequency within infected cells [41].

All cells acquire DNA damage as they transit the cell cycle. DNA damage that exists in the first growth phase, G_1, of the cell cycle can be repaired by DNA repair mechanisms including base excision repair (BER), nucleotide excision repair (NER), recombination and direct repair of nicks by DNA ligation. The first indication that Tax might affect DNA repair was provided in 1990 when Tax was shown to repress transcription from the human DNA polymerase β promoter, an enzyme involved in BER [21]. It has since been shown that the HTLV-I Tax protein does decrease BER in viral-transformed cells and transient transfections [48]. Two retroviruses that are most closely related to HTLV-I, HTLV-II and bovine leukemia virus, both encode Tax proteins that inhibit BER [48]. Although HTLV-II has not been definitively associated with a human cancer, the HTLV-II Tax protein can transform cells in culture. Bovine leukemia virus causes an acute B cell leukemia in cattle, and the bovine leukemia virus Tax protein can also transform cells in culture. Thus, it appears that the ability of these Tax proteins to inhibit BER may contribute to their transforming function in cell culture, although additional events or functions may be required for the development of leukemia.

More recently, HTLV-I Tax was shown to suppress NER following UV irradiation of rat fibroblasts [24]. NER requires the activity of DNA polymerases δ and ε, both of which utilize the trimeric sliding clamp cofactor proliferating cell nuclear antigen (PCNA). In the presence of DNA damage, elevated levels of the cdk inhibitor p21 allow it to interact directly with PCNA and block PCNA-dependent DNA replication, without interfering with PCNA-dependent DNA repair [67] (fig. 1). Excess PCNA can overcome the p21 block of DNA replication [33], allowing DNA polymerase δ synthesis past template lesions and resulting in increased nucleotide misincorporation rates [43]. Tax inhibition of NER was shown to correlate with its ability to transactivate the PCNA promoter [28] and has subsequently been shown to depend, at least in part, on its ability to functionally inactivate p53 [25]. Reports to date suggest that Tax does not interfere with DNA ligation [48], and there is no evidence that Tax affects recombination activity. However, given the redundancy of these DNA repair pathways, additional studies will be required to specifically rule out a role of Tax in ligation- or recombination-mediated repair.

Several other functions of Tax contribute to its ability to inhibit DNA repair and fix mutations in the genome. In order for a DNA lesion to be fixed into the genome as a

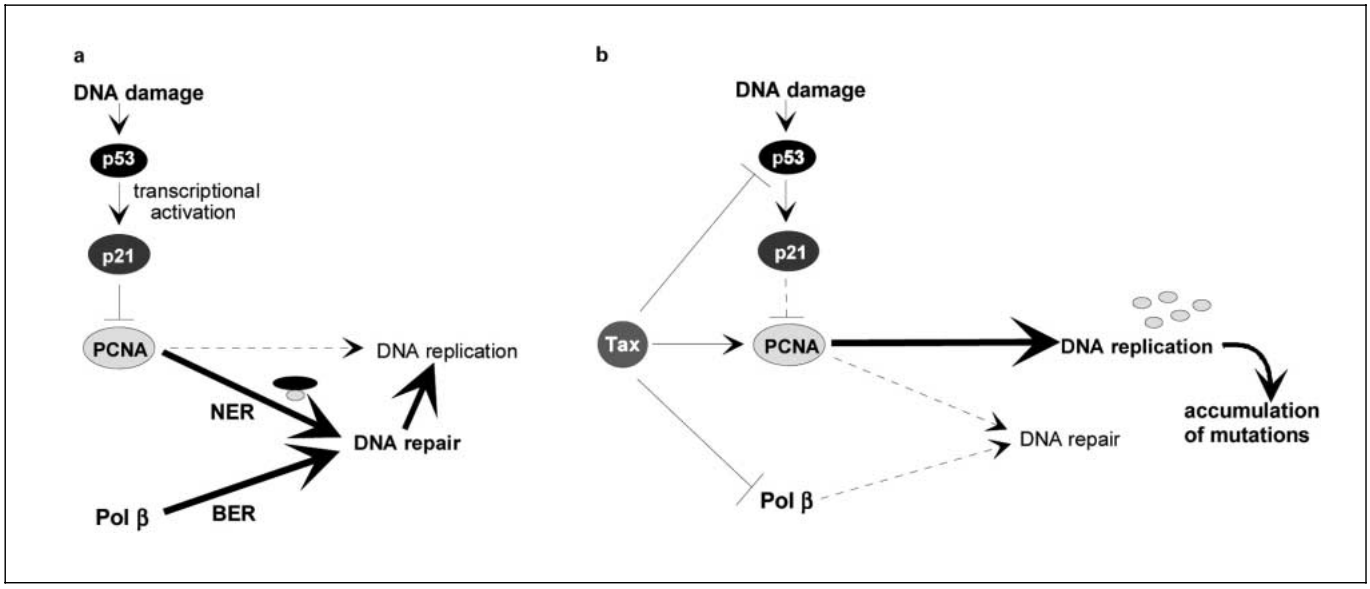

Fig. 1. Effect of Tax on DNA repair and replication. a A normal cell responds to DNA damage by inducing p53 expression. p53 then transcriptionally activates a group of cellular genes, including p21. p21 forms a complex with PCNA that blocks DNA replication and promotes NER. Polymerase β (Pol β) promotes BER. Once repair is complete, DNA replication proceeds. b In an HTLV-I-infected cell expressing Tax, p53 function is inactivated and polymerase β (Pol β) transcription is repressed by Tax, thereby reducing both NER and BER. Although p21 levels may be elevated through other mechanisms, it is not clear whether this p21 is functional. Tax activation of PCNA expression stimulates DNA replication even in the presence of DNA damage. This activity, coupled with the loss of G_1/S checkpoint control, results in the accumulation of mutations in the host genome.

mutation, the lesion must not be repaired, the cell that contains damage must not die and the DNA that contains the lesion must be successfully replicated to introduce the mutation. The ability of Tax to simultaneously suppress DNA repair, stimulate cell cycle progression and block apoptosis should result in the introduction of mutations into the genome. In fact, genetic evidence has demonstrated that these combined biological effects of Tax result in a 2.8-fold increase in genomic mutation frequency [41]. Also contributing to the disruption of DNA repair pathways, Tax has been shown to inhibit protective cellular mechanisms that stabilize the ends of DNA breaks [39]. Taken together, the effects of Tax on BER, NER, DNA end stability and cell cycle progression create a cellular environment in which the repair of DNA damage is compromised. This mechanism, termed the mutator phenotype, is thought to be a relatively common and critical component of cellular transformation.

HTLV-I Tax and Aneuploidy

The genome integrity of human diploid cells mandates precise and reproducible partitioning of chromosomes from one mother cell to two daughter cells. During mitosis, 23 pairs of condensed human chromosomes align at the metaphase plate in preparation for impartial segregation to opposite poles of the dividing cell. If unequal division of chromosomes occurs as one mother nucleus transits to two daughter nuclei, aneuploidy ensues. Studies over the last several years have shown that perturbation of several discrete pathways can lead to aneuploidy [7, 10, 35, 58]. Recently, the mitotic spindle assembly checkpoint (MSC) has been recognized as an important guardian of euploidy.

Genetic studies in yeast and mammals have implicated at least 7 genes [19, 31] in MSC function, i.e. Mps1 (monopolar spindle) [1, 9], BUB (budding uninhibited by benomyl) 1, 2 and 3 and MAD (mitotic arrest deficiency) 1, 2 and 3 (fig. 2). These MAD, BUB and Mps1 proteins form complexes that regulate orderly chromosomal segregation in mitosis. Should spindle damage or segregation mis-

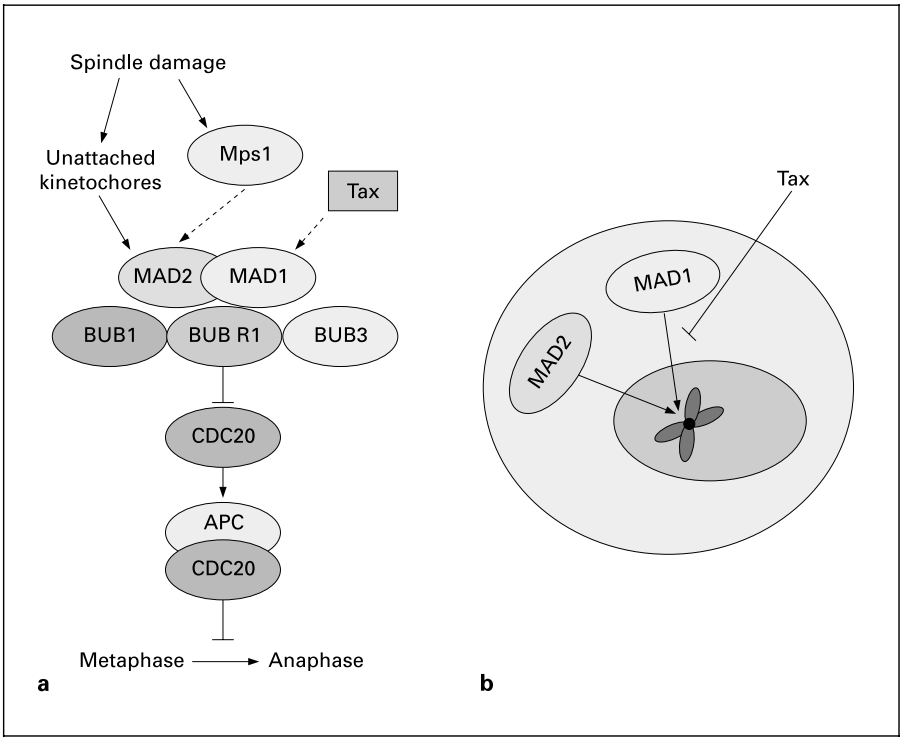

Fig. 2. Interaction of HTLV-I Tax with the MSC. a Some of the characterized components of the mammalian spindle assembly checkpoint, which regulates metaphase to anaphase progression. Tax was found to be a direct binding protein for the MAD1 checkpoint factor. APC = Anaphase-promoting complex. b The role of MAD1 in directing MAD2 to kinetochores. One way through which Tax interferes with MSC function is to interrupt the localization of the MAD1/MAD2 complex to kinetochores.

takes occur, the MSC is activated to arrest metaphase-to-anaphase transition in order to prevent propagation of error [69]. Missegregations can be corrected, relieving arrest and permitting further progression in mitosis. In cases of irreparable errors, the correctly functioning MSC signals the initiation of apoptosis such that errors are not transmitted to progeny nuclei. The details of how the MSC works are still not fully understood. Currently, it is generally agreed that the distal effector protein of the metaphase-anaphase checkpoint is MAD2, which binds CDC20 and inhibits the function of the anaphase-promoting complex [8, 34, 68].

The connection between HTLV-I and MSC function was identified several years ago by the demonstration that Tax directly bound the human MAD1 protein and inactivated its checkpoint function [22]. Recently, the generality of this finding was extended by demonstration that virtually all HTLV-I-transformed cells are defective in the MSC [26] (fig. 2). Mechanistically, binding of the spindle effector protein, hsMAD2, to kinetochores is a critical step in mitotic checkpoint function. It has been shown that intact MAD1 function is needed to direct MAD2 to kinetochores [5]. In the presence of Tax, the MAD1 protein becomes mislocalized from the nucleus to the cytoplasm [26]. Loss of MAD1 function affects the ability of MAD2 to locate properly to kinetochores, leading to a loss of MSC function.

There may be a second connection between HTLV-I Tax and MAD1. The *hsMad1* transcript was originally found, as p53-induced gene 9 *(PIG9),* to be one of only fourteen cellular mRNAs that were robustly induced by a p53-expressing adenovirus vector in the colorectal cancer line DLD-1 [52]. Mutation of p53 is the most common genetic alteration found in human cancers [18], and several studies have linked aberrant cellular ploidy with p53 mutations [14, 44]. Interestingly, a plethora of evidence documents the ability of the HTLV-I Tax protein to inactivate cellular p53 function [2, 25, 38, 62, 65, 66]. One could envision a scenario in which p53-dependent MAD1 induction is abrogated by HTLV-I Tax through inactivation of p53 activity. More experimental support is needed to fully confirm this hypothesis. However, if this line of reasoning holds, it means that Tax can affect MAD1/MSC in two independent ways: directly, through protein-protein contact, and indirectly, through abrogation of p53 function. This bimodal disruption of MSC by Tax may be one reason for the virtually universal presence of aneuploidy in ATL cells [59].

Conclusions and Future Directions

Accumulating evidence suggests that malignant transformation is a multi-hit phenomenon and that chromosomal aberrations and genome instability play causal roles in tumor development and progression [3, 27]. In this brief review, we have highlighted two mechanisms through which the HTLV-I Tax protein facilitates the accumulation of genetic lesions that contribute to cellular transformation: inhibition of DNA repair and chromosome missegregation. These mechanisms both involve induction of a mutator phenotype [37] that promotes an increased mutation rate. In the case of HTLV-I, the relationship between age and disease onset suggests that approximately five independent genetic events are required for the development of ATL [46]. Thus, numerous studies have converged on the idea that Tax plays a critical role in the fixation of these DNA mutations within the genome of HTLV-I-infected cells.

It is interesting to note that the clastogenic and aneuploidogenic effects of Tax are predominately indirect. That is, Tax does not affect the introduction of mutations into the genome nor does it cause chromosome missegregation. Rather, Tax inactivates cell cycle checkpoint controls such that cellular DNA repair cannot be completed and DNA replication or chromosomal segregation occurs in the presence of damage. Thus, damage becomes fixed in the genome as inherited mutations. Interestingly, inhibition of the p53 cell cycle checkpoint regulator appears to play a role in both the clastogenic and aneuploidogenic effects of Tax.

The effects of Tax are focused predominantly in the G_1/S and G_2/M phases of the cell cycle. Events at these two points in the cell cycle result in different, but complementary types of DNA damage, i.e. point mutations (G_1/S) and chromosomal missegregation (G_2/M), which together contribute to the abundant accumulation of mutations observed in ATL cells. Thus, Tax induces a mutator phenotype by altering the cellular environment such that reduced DNA repair capacity and increased ability to replicate through DNA damage favors the accumulation of DNA mutations and chromosomal aberrations. This environment provides a solid foundation for subsequent steps in HTLV-I transformation such as the deregulation of cellular oncogenes or tumor suppressors by these chromosomal alterations.

What evolutionary advantage might these activities provide the virus? HTLV-I is poorly infectious as a cell-free virus; thus, its successful replication is directly dependent on cell viability and proliferation. Since the CD4+ T cell target for HTLV-I typically exists as a nondividing cell in the infected host, it is critical for this virus to have evolved a mechanism to stimulate cell proliferation. The inhibition of DNA repair function in Tax-expressing cells probably results indirectly from the inactivation of cell cycle checkpoints, thus allowing the cell to proceed through the cell cycle before completing important tasks such as genome surveillance and DNA repair. These arguments suggest that the transforming ability of Tax is an unintentional and rare by-product of efforts to create a cellular environment that optimizes virus replication.

The random nature of chromosomal damage predicted by this model explains the low occurrence of ATL in infected individuals as well as the long and variable period of clinical latency that precedes the onset of ATL. The presence of excessive DNA damage typically signals a cell to die by apoptosis. However, studies outside the scope of this review suggest that Tax can suppress apoptosis under these circumstances, providing yet another supportive mechanism for the survival of cells containing fixed genetic damage. Future studies will be required to define the precise nature of the loss of G_1/S and G_2/M checkpoint control in Tax-expressing cells and to determine the ultimate role of specific genetic lesions in the development of ATL.

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